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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	16

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/294,980	Applicant(s) DOLLY ET AL.	
	Examiner Anne M. Baker	Art Unit 1632	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 April 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,9,11 and 13-24* is/are pending in the application.

4a) Of the above claim(s) *11,13-15 and 17-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,9 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

The response filed April 23, 2001 (Paper No. 15) has been entered. The amendments filed July 12, 1999 (Paper No. 5) and October 2, 2000 (Paper No. 11) have been entered. Claims 1 and 13-24 have been amended. Claim 7, 8, 10, and 12 have been cancelled.

Claims 1-6, 9, 11, and 13-24 are pending in the instant application.

Applicants' election with traverse of the CNTF species and Group III, Claims 1-6, 9, 11, and 13-24, in Paper No. 15 is acknowledged. Applicants argue that the election of species requirement is improper because the claims are not directed to the proteins themselves. However, the claims are directed to methods of inhibiting the activity or expression of the proteins recited in the claims, with a variety of different classes of molecules. The proteins are not obvious variants nor are they homologous proteins. Thus, a compound that inhibits the activity or expression of one protein would not be expected to inhibit the activity of the other proteins recited in the claims. Each protein or the gene encoding each protein must be specifically inhibited by separate and distinct agents. Applicants argue that antisense agents directed to the promoter and regions encoding the N-terminal residues of these proteins, while not necessarily identical would have a common utility and share substantial structural features, in that they would all contain a nucleotide sequence complementary to the ATG start codon. However, there is no evidence of record that these genes have the same promoters nor that the promoters are highly homologous. Furthermore, a nucleotide sequence complementary to the ATG start codon would not be considered a substantial structural feature, as the inhibition that is sought is intended to be specific and thus would require much more than this to accomplish specific inhibition. Nearly all protein-encoding genes have an ATG codon. There is no evidence of record that the proteins recited in the claims or the genes encoding them could be inhibited by a common strategy

using common inhibitory agents. Each protein and the gene encoding each protein requires a separate and distinct method, using separate and distinct agents, for their inhibition. Thus, methods for inhibiting each protein or the gene encoding each protein are distinct and independent inventions.

The requirement is still deemed proper and is therefore made FINAL.

The elected invention is directed to a method for extending the effective time tissue is paralyzed with a clostridial toxin comprising administering an agent that prevents the expression of a ciliary neurotrophic factor (CNTF) gene. It is noted that Claims 11, 13-15, and 17-24 are directed to non-elected species and thus, are not examined herein. It is further noted that Claims 1-6 and 9 encompass non-elected subject matter. Thus, Claims 1-6 and 9 are examined herein only to the extent that they encompass the elected subject matter.

Claims 11, 13-15, and 17-24 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected species, the requirement having been traversed in Paper No. 15.

Claims 1-6, 9, and 16 are examined herein.

Specification

This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art

to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 9, and 16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the full scope of the claimed invention. Applicants are referred to the revised interim guidelines on written description published December 21, 1999 in the Federal Register at Volume 64, Number 244, pp. 71427-71440 (also available at www.uspto.gov).

The claims are directed to a method for extending the effective time tissue is paralyzed with a clostridial toxin comprising administering an agent that prevents the expression of a ciliary neurotrophic factor (CNTF) gene. However, the specification does not disclose any agent that can be used in the claimed method. In the absence of a written description of the inhibitory agent, the claimed method lacks written description because the inhibitory agent is an essential element of the claimed method. The specification does not disclose the nucleotide sequence of any ribozyme or antisense molecule that can be used to inhibit the expression of a CNTF gene, nor does the specification disclose any other agent that can be used to inhibit the expression of a CNTF gene. In Example 3, the specification discusses the use of a ribozyme directed to neural agrin mRNA, but the nucleotide sequence of this ribozyme is not disclosed. In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In this case, no CNTF gene inhibitor is disclosed. Next then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. In this case, only general teachings are provided for the development of antisense and ribozyme molecules. While the skilled artisan may develop a variety of molecules using these general guidelines, there is insufficient guidance regarding which molecules will

function *in vivo* in the manner intended. This limited information regarding the contemplated embodiments is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of the full scope of agents for the inhibition of CNTF gene expression. Thus, it is concluded that the written description requirement is not satisfied for methods of using the genus of agents recited in the claims.

Claims 1-6, 9, and 16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a method for extending the effective time tissue is paralyzed with a clostridial toxin comprising administering an agent that prevents the expression of a ciliary neurotrophic factor (CNTF) gene. While the claims encompass the use of any agent to inhibit the expression of CNTF genes, the specification only explicitly contemplates the use of antisense and ribozymes. The specification does not provide any teachings for the use of agents other than antisense or ribozymes. Thus, the enablement rejection advanced herein below is directed specifically to the use of antisense and ribozymes, but applies broadly to the use of any agent that will inhibit the expression of a CNTF gene.

The specification fails to provide an enabling disclosure for the method comprising inhibiting the expression of CNTF genes because the *in vivo* function of antisense and ribozymes is unpredictable. Furthermore, as discussed above only general teachings are provided for the design of ribozyme and antisense molecules. No specific molecules are disclosed. Moreover, the specification does not teach how to use a ribozyme molecule that specifically cleaves CNTF mRNA or an antisense molecule that specifically inhibits CNTF expression. The specification only teaches a single mode of delivery wherein the antisense or ribozyme molecule is conjugated to the clostridial toxin. However, the claims specifically recite

administering the ribozyme or antisense nucleic acid prior to the administration of clostridial toxin, but the specification does not teach how to deliver the antisense or ribozyme nucleic acid when not linked to the toxin. The specification discusses neural agrin mRNA-specific ribozymes (though it does not teach their nucleotide sequence), but does not teach ribozymes specific for CNTF mRNA. Dietz (US Patent No. 5,814,500) teaches that many studies with antisense show that gene expression is suppressed by 80-90% of the normal level, but that such reduction is not typically sufficient to reduce the biological effect, i.e., 10-20% expression is sufficient to maintain the biological function sought to be suppressed. The same is true for ribozymes. Baier et al. (1994) also reveal that significant reduction in target mRNA levels as a consequence of ribozyme activity is often not accompanied by reduced expression of the corresponding target protein (last sentence of Abstract and p. 930, column 1, paragraphs 2 and 3). Thus, it is not a routine matter to design antisense and ribozyme molecules appropriate to induce the degree of inhibition necessary to produce the desired effect. Varying degrees of *in vivo* stability of the hybrid leads to varying degrees of inhibition. Accordingly, the *in vivo* effect of any particular ribozyme construct or antisense molecule cannot be predicted. Thus, the success of the method for inhibiting CNTF gene expression *in vivo* relies on the specific design of the antisense or ribozyme construct. In the absence of specific guidance, one skilled in the art would not know how to design ribozymes or antisense targeted to any gene, including those targeted to CNTF mRNA, to achieve a desired level of expression inhibition to produce a desired effect. Furthermore, the operability of the claimed method *in vivo*, in any animal, depends on a number of factors. Good et al. (1997) disclose that the effective intracellular expression of small RNA therapeutics, whether antisense, ribozyme, or RNA aptamer, requires that the RNA be efficiently transcribed, stabilized against rapid degradation, folded correctly, and directed to the part of the cell where it can be most effective (Abstract). The specification does not provide specific guidance for inhibiting CNTF gene expression. Thus, the specification does not teach

how to produce the desired effect *in vivo* using ribozyme and antisense constructs. In the absence of specific guidance, for producing the desired effect as a consequence of the introduction of a ribozyme or antisense construct, one skilled in the art would not know how to use the claimed method. Furthermore, in the absence of specific guidance regarding the design of a ribozyme or antisense molecule to produce a desired effect, one skilled in the art would not know how to make the compositions necessary for use in the claimed method.

Given that specific effects cannot be predictably achieved by merely transferring a ribozyme or antisense nucleic acid into a tissue, specific guidance must be provided in the disclosure to enable the instant invention. The specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. The claims encompass a method for controlling the expression of a CNTF gene in any animal, but the specification does not enable such a method. Given the limited working examples, the broad scope of the claims, the limited guidance in the specification, and the unpredictability of ribozyme and antisense design for *in vivo* applications, undue experimentation would have been required to practice the claimed method.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6, 9, and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-6, 9, and 16 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: treating the tissue with a clostridial toxin. The claims recite a "method for extending the

effective period during which tissue treated with a clostridial toxin is paralyzed" but the method recites only the step of contacting the tissue with the inhibitory agent. The preamble is in conflict with the recited steps. The claims further recite "wherein neural sprouting in said treated tissue is inhibited" but the specification does not teach that neural sprouting can be inhibited by treating a tissue with an inhibitor of CNTF expression alone, in the absence of treatment with a clostridial toxin.

Claims 1-6, 9, and 16 are indefinite because the claims encompass non-elected subject matter.

Claims 1-6, 9, and 16 are indefinite in their recitation of "neural sprouting" because it is unclear what specific biological activity is being inhibited. At page 10, the specification states:

> First, the poisoned endplate becomes synaptically inactive. Shortly thereafter the endplate elaborates thin nascent axon neural processes. These processes or "sprouts" are synaptically competent after about 14 days following treatment with clostridial neurotoxin. The sprouts continue growing, reaching a maximal length and level of complexity after about 42 days following treatment with neurotoxin. During this time, the endplate remains synaptically inactive.

However, it is unclear whether "sprouting" refers to the point at which the processes initially appear or the continued growth of the sprouts or both. The specification does not define the term "neural sprouting". Thus, the metes and bounds of the claims are not clearly set forth.

Conclusion

No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Baker whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached on (703) 305-6608. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Kay Pinkney, whose telephone number is (703) 305-3553.

Anne-Marie Baker, Ph.D.

Anne-Marie Baker

ANNE-MARIE BAKER
PATENT EXAMINER